

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election with traverse of atopic dermatitis in the reply filed on December 7, 2007 is acknowledged. The traversal is on the ground(s) that all of the conditions may be treated with the composition of claim 1 and that an examination fee has been paid for all of the claims. This is not found persuasive because while the conditions may be treatable by the same composition, the causes, etiologies and symptoms of all of the listed diseases are not the same.

The requirement is still deemed proper and is therefore made FINAL.

### ***Status of Claims***

Claims 1 – 37, 49, 64, 65, 68 – 71, 74, 75 and 77 – 79 are currently pending. Claims 31 and 32 are withdrawn from consideration as not being drawn to the elected invention. Claims 1 – 30, 33 – 37, 49, 64, 65, 68 – 71, 74, 75 and 77 – 79 are currently under examination.

### ***Claim Rejections - 35 USC § 112 1<sup>st</sup> Paragraph***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 37 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of steroid responsive disorders, does not reasonably provide enablement for the treatment of diseased tissue in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The disclosure and claims of the application have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation

The factors include:

1. The nature of the invention;
2. The breadth of the claims;
3. The predictability or unpredictability of the art;
4. The amount of direction or guidance presented;
5. The presence or absence of working examples
6. The quantity of experimentation necessary;
7. The state of the prior art; and
8. The relative skill of those skilled in the art.

Each factor is address below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1. The nature of the invention: A method of treating diseased tissue in a mammal comprising the topical administration of a pharmaceutical composition comprising a  $\alpha$ -hydroxy acid, the corticosteroid prednicarbate and a pyrrolidone carboxylate salt.

2. The breadth of the claims: Any diseased tissue that can occur in a mammal is encompassed by these claims.

3. The amount of direction or guidance presented, the presence or absence of working examples: A pharmaceutical composition is presented. Examples of various skin conditions (examples 2 – 24) such as pruritus, chronic and acute chronic eczema and atopic dermatitis are provided. The administration of the pharmaceutical composition in each of these examples is "expected that the patient would improve his/her condition or recover".

4. The predictability or unpredictability of the art, the quantity of experimentation necessary, the state of the prior art, and the relative skill of those skilled in the art: The relative skill of those skilled in the art is high. Prednicarbate is known for the treatment of inflammation and pruritus associated with corticosteroid responsive dermatological disorders such as dermatitis and eczema (p 62, paragraph 1, Spencer and Wagstaff,

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BioDrugs, 9(1), p 61-86, 1998). However, the claims encompass any diseased tissue in a mammal. This includes conditions such as gangrene, cancer, arthritis and heart disease. There is no indication that a topical pharmaceutical composition comprising the corticosteroid prednicarbate would be efficacious in the treatment of all diseased tissue in a mammal.

Therefore, Applicant is enabled for the treatment of corticosteroid responsive dermatological disorders such as dermatitis and eczema but is not enabled for the treatment of any and all diseased tissue in mammals.

***Claim Rejections - 35 USC § 112 2<sup>nd</sup> Paragraph***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 – 27, 49, 64, 65, 68 – 71, 74, 75 and 77 – 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims contain the phrase “less than about 10%”. “Less than” indicates a maxima and all possible values below 10% are included. “About” indicates a range centered on 10%, including values both above and below 10%. Therefore what values are included in the claims cannot be determined.

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6. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of multiple ands, the comma and the backslash in this claim make it unclear whether the list of chemical names form a Markush group of items that may be selected from to form a combination of emulsifiers or if the combination of emulsifiers claimed includes all 4 of items recited. This has been treated as a Markush group for the art rejections presented below.

7. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim contains the limitation “wherein the composition is formulated for pediatric use.” What characteristics of a composition make it suitable for pediatric use are not defined and therefore the metes and bounds of the claim cannot be determined.

8. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim contains the limitation “wherein the composition is administered to sensitive skin.” “Sensitive skin” is not defined and therefore the metes and bounds of the claims cannot be determined.

9. Claims 49, 64 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

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which applicant regards as the invention. A Markush group of possible oily material is presented. The list concludes with “and mixtures thereof and at least two emulsifiers.” A mixture by definition includes at least two ingredients so it is unclear whether “at least two emulsifiers” is another item present in the Markush group or if it is a completely separate option that is not included in the Markush group.

10. Claim 78 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim contains the limitation “wherein said composition exhibits chemical and physical stability suitable for topical administration.” What stability characteristics are required to make a composition suitable for topical administration are not defined and therefore the metes and bounds of the claim cannot be determined.

### ***Claim Rejections - 35 USC § 103***

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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12. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 1 – 13, 15, 17 – 20, 24 – 30, 33 – 37, 49, 64, 65, and 77 – 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murad (PGPub 2002/0054918) in view of Spencer and Wagstaff.

Murad discloses pharmaceutical compositions for the prevention, treatment and management of inflammatory skin conditions such as atopic dermatitis (paragraph [0028]). These compositions comprise a moisturizing agent (paragraph [0022]) and optionally, and exfoliant such as alpha-hydroxy acids (paragraph [0023]). The moisturizing agents are typically present in an amount from about 0.01 to 20 weight percent (paragraph [0032]). Exemplified as a hydrophilic moisturizing agent is sodium peroxylinecarboxylic acid (sodium PCA, (paragraph [0032]). In example 1 (paragraph [0066]), this compound is also known by the trade name AJIDEW-50®. As evidenced by CAS Registry record 28874-51-3, AJIDEW-50® is another name for the sodium salt of 2-pyrrolidinone-5-carboxylic acid. The alpha-hydroxy acid citric acid is present in part B of example 1, which is mixed with the aqueous part A (paragraph [0067]). The pyrrolidone carboxylate salt PCA is present in the aqueous part D (paragraph [0066]).

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The mixing of the composition takes place in a processing tank (paragraph [0067]). In this composition, the pH of the final solution was between 4 and 4.5 (paragraph [0067]).

In Example 3 (paragraph [0070]), sorbitan stearate is present in part B of the composition. Sorbitan stearate is an emulsifier that is an ester the fatty acid stearic acid and sorbitan. Part A is an aqueous component and these two components are mixed until uniform (paragraph [0071]). The pH of this composition was adjusted to 6.2 to 7.2.

The poly-hydroxy acid component can be an alpha-hydroxy acid such as citric or lactic acid (paragraph [0040]). This component is typically present in amounts ranging from about 0.1 to 12 weight percent (paragraph [0042]). The compositions can further comprise ingredients such as anti-oxidants, buffering agents, emulsifying agents and thickeners (paragraph [0044]). Dosage forms for the composition include lotions, creams, ointments and oil-in water or water-in-oil emulsions (paragraph [0060]).

Murad does not disclose the use of a corticosteroid such as prednicarbate in the pharmaceutical compositions.

Spencer and Wagstaff disclose the use of prednicarbate for the relief of inflammation and pruritus associated with corticosteroid responsive disorders such as atopic dermatitis and psoriasis (p 62, paragraph 5). Suitable formulations of the drug include creams, solutions and ointments (p 62, paragraph 5). Available formulations of prednicarbate include 0.25% or 0.1% of prednicarbate (p 64, paragraph 8). The use of prednicarbate for the treatment of children with such conditions is also discussed (p 78, section 3.1.3).

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“It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06**.

Together, Murad and Spencer and Wagstaff teach a pharmaceutical composition comprising an alpha-hydroxy acid such as lactic acid, a pyrrolidone carboxylate salt such as sodium pyrrolidone carboxylate and prednicarbate that is suitable for the treatment of atopic dermatitis. Patients with atopic dermatitis suffer from chronically inflamed skin and because of that, their skin is sensitive. The pH of the solution taught by Murad was between 4 and 4.5. The amount of the acidic form and the salt form present in a particular solution is described by the Henderson-Hasselbalch equation, shown below, wherein  $[A^-]$  is the concentration of salt form and  $[HA]$  is the concentration of the acidic form:

$$\text{pH} = \text{pK}_a + \log_{10} \frac{[A^-]}{[HA]}$$

For the composition in example 1 of Murad, the alpha-hydroxy acid was citric acid. The  $\text{pK}_a$  of this compound is 2.90 (CAS Registry entry for citric acid, page 7). If the pH of the solution was 4.0, then the ratio of  $[A^-]/[HA]$  is approximately 12. Therefore, in this composition, the alpha-hydroxy acid is present as a mixture of mixture of an acid and a salt.

It is obvious to one of ordinary skill in the art to use ingredients to use ingredients that are of a high purity and contain minimal amounts of decomposition products, particularly for those ingredients that impart the therapeutic effectiveness to the composition and are not present as excipients. By using ingredients with high levels of impurity, one is adding less of the active ingredient than one might calculate since some of the ingredient has decomposed. Additionally, those decomposed products may result in unwanted characteristics, such as side effects when the composition is applied or discoloration of the composition. Therefore, it would be obvious to one of ordinary skill in the art to formulate the composition using an alpha-hydroxy acid that is at least 90% pure to avoid these undesirable characteristics.

The composition is prepared in a processing tank, a suitable containment vessel. The mixing, storage, shipping and delivery of such products to consumers require some sort of container to contain the product. It would be obvious to one of ordinary skill in the art to place the final product in smaller containment vessels for the purposes of storage and sales. A number of materials would be suitable for storage and sale of the composition and such materials would also be obvious to one of ordinary skill in the art.

Claims 77 and 78 are product-by-process claims. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ

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964, 966 (Fed. Cir. 1985) (citations omitted) **MPEP 2113**. There is no indication that the described process of manufacture results in a patentably distinct product when compared to that described by the prior art.

Therefore the combined teachings of Murad and Spencer and Wagstaff renders the claims of the instant application obvious to one of ordinary skill at the time of the instant invention.

14. Claims 12 – 14, 16, 21 – 23, 68 – 71, 74 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murad and Spencer and Wagstaff as applied to claims 1 – 13, 15, 17 – 20, 24 – 30, 33 – 37, 49, 64, 65, and 77 – 79 above, and further in view of Sine et al. (US Patent 5,972,359).

As discussed above, Murad and Spencer and Wagstaff teach topical pharmaceutical compositions comprising prednicarbate, alpha-hydroxy acids and sodium pyrrolidone carboxylate. They do not provide exhaustive lists of emulsifiers that may be used in these compositions. They do not explicitly teach the adjustment of the pH of the compositions using acids and/or bases that may contain hydroxyl groups.

Sine et al. discloses topical compositions for improving the appearance or other condition of the skin (col 1, ln 8 – 10). A preferred carrier for active ingredients in these formulations is an emulsion with a hydrophilic and hydrophobic or oily phase (col 6, ln 54 – col 7, ln 12). Emulsifiers/surfactants that may be added to the emulsion (col 12, ln 25 – 32) include stearyl alcohol (col 12, ln 59), glyceryl stearate (col 14, ln 25), polyoxyethylene 20 sorbitan trioleate (col 14, ln 25 – 26), polyoxyethylene 4 lauryl ether

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sodium stearate (col 14, ln 26 – 27), sorbitan monolaurate (col 14, ln 26), and fatty acid esters blends based on a mixture of sorbitan or sorbitol fatty acid esters and sucrose fatty acid esters (col 14, ln 30 – 33). In examples 1 – 3 (beginning at the bottom of col 38), the hydroxyl group containing base sodium hydroxide (NaOH) is present in Phase E. It is used to modify (neutralize) the pH of the composition. Preservatives are indicated as optional ingredients (col 24, ln 1).

To prepare the compositions in examples 1 – 3, the ingredients in phases A, B and C are mixed together. The oily ingredients in Phase D are mixed in a separate container and both mixtures are heated to 75°C. Then the Phase A/B/C mixture is combined with phase D until a homogeneous mixture is formed. Given the ingredients used, this mixture will be an emulsion. Then Phase E, containing the pH adjusting agent NaOH is added to the mixture. After cooling the mixture to a temperature of about 50°C, additional ingredients are added. The mixture is further cooled to 40°C and additional ingredients are added. The mixture is further cooled to 30°C and the phase H ingredients, including an active ingredient (retinol), are added to the mixture (col 39, ln 1 – 59). The polymer thickeners CARBOPOL® and the emollient glycerin are included in the prepared composition.

The exact order and solubilization steps recited in the claims are not taught by Murad, Spencer and Wagstaff or Sine et al. but do given generic teachings for the process of making an emulsion. The method described in Sine et al. includes the additional of the active ingredients prior to the formation of the emulsion (the tocopheryl acetate in phase D) as well as after the emulsion has been formed (retinol in Phase H).

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While the pH of the aqueous phase is not adjusted prior to the formation of the emulsion, the pH is adjusted prior to the final composition. The latter method is the method of adjusting the pH that is described in Murad. As to the exact order of the additions of the active ingredients and when the pH of phase or final composition is adjusted, it is within the skill of one of the ordinary skill to determine the exact order and steps needed to prepare a composition.

The combined teachings of Murad, Spencer and Wagstaff and Sine et al. renders obvious the claims of the instant application to one of ordinary skill in the art at the time of the instant invention.

### ***Conclusion***

Claims 1 – 30, 33 – 37, 49, 64, 65, 68 – 71, 74, 75 and 77 – 79 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 7:30 a.m. - 5 p.m. ET. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718 or Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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NMW

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